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**Datasheet for the decision
of 6 July 2010**

Case Number: T 1293/06 - 3.3.02

Application Number: 97948461.5

Publication Number: 0941095

IPC: A61K 31/545

Language of the proceedings: EN

Title of invention:
Improved pharmaceutical compositions

Patentee:
Pharmacia & Upjohn Company LLC

Opponent:
CABINET ORES

Headword:
Improved pharmaceutical compositions/UPJOHN

Relevant legal provisions:
EPC Art. 56

Relevant legal provisions (EPC 1973):

-

Keyword:
"Inventive step (no): Effect not credible over the scope of product claim, arbitrary choice of quantity of component"

Decisions cited:

-

Catchword:

-



Case Number: T 1293/06 - 3.3.02

D E C I S I O N
of the Technical Board of Appeal 3.3.02
of 6 July 2010

Appellant: Pharmacia & Upjohn Company LLC
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Decision under appeal: Decision of the Opposition Division of the
European Patent Office posted 30 June 2006
revoking European patent No. 0941095 pursuant
to Article 102(1) EPC 1973.

Composition of the Board:

Chairman: U. Oswald
Members: H. Kellner
J.-P. Seitz

Summary of Facts and Submissions

- I. European patent No. 0 941 095, based on international application PCT/US1997/021401 published as WO 1998/025621 and having application No. 97 948 461.5 in the EPO, was granted with 10 claims.

Independent claim 1 as granted read as follows:

"A pharmaceutical composition comprising ceftiofur hydrochloride, a biocompatible oil, and 0.5 to 200 mg/ml water."

- II. Opposition was filed against the granted patent under Article 100(a) EPC (novelty and inventive step), Article 100(b) EPC (added subject-matter) and 100(c) EPC (sufficiency of disclosure).

The documents cited during the proceedings before the opposition division and the board of appeal include the following:

(2) US 4 902 683

(11) US 5 721 359

(12) "Etude de l'influence de la teneur en eau sur la stabilité de suspensions huileuses de chlorhydrate de ceftiofur" filed by the respondent with fax dated 17 March 2006

(14) "Declaration of Nancy J. Britten, submitted by the patentees", signed on 11 April 2006 and filed by fax of 11 May 2006

(20) "Bilan au bout de trois mois d'étude" filed by the respondent with fax dated 16 May 2006

III. By its decision posted on 30 June 2006, the opposition division revoked the patent under Article 102(1) and (3) EPC 1973.

The opposition division held that the set of claims of the request as filed met the requirements of Articles 123(2), 83 and 54 EPC.

Closest prior art was the oily composition of ceftiofur hydrochloride identified in the patent specification as "EXCENEL® sterile suspension" and the compositions as claimed differed from "EXCENEL® sterile suspension" in that they comprised a water content ranging from 2.5 to 22 mg/ml of the composition.

The problem to be defined was to provide an oily ceftiofur hydrochloride pharmaceutical composition with improved physical and chemical properties.

The opponent had, however, provided technical data which showed that at least one pharmaceutical composition falling under the terms of claim 1 did not solve the problem posed. Thus, the technical problem was not solved in the whole scope of the claim and the requirements of Article 56 EPC were not met.

IV. The appellant lodged an appeal against that decision and filed grounds of appeal together with a request that the patent be maintained according to its main or

its auxiliary request. The main request corresponds to the sole request before the opposition division.

With its letter of 15 January 2010, it filed two further sets of claims as second and third auxiliary requests together with further documents; with letter of 17 June 2010, an amended second auxiliary request was submitted.

Claim 1 of the main request differs from claim 1 as granted, in particular with regard to the definition of the range of water being present. It is worded as follows:

"A pharmaceutical composition comprising ceftiofur hydrochloride, a biocompatible oil, and 2.5 to 22.0 mg of water/ml of composition."

In claim 1 of the first auxiliary request, this range is narrowed to "2.5 to 7.5 mg of water/ml of composition".

In claim 1 of the second auxiliary request, with respect to the main request two excipients are added (amendments in bold):

"A pharmaceutical composition comprising ceftiofur hydrochloride, a biocompatible oil, **lecithin, sorbitan monooleate** and 2.5 to 22.0 mg of water/ml of composition."

Claim 1 of the third auxiliary request is worded as follows:

"An oil suspension of ceftiofur hydrochloride comprising an effective amount of ceftiofur hydrochloride, a biocompatible oil, and one or more pharmaceutically acceptable excipients characterized by an amount of water of 0.25% to 2.20% of the suspension."

V. On 6 July 2010, oral proceedings took place before the board.

VI. The appellant's submissions may be summarised as follows:

Novelty objections could not be derived from the combination of two documents, or on theoretical assumptions as to what relations of components might exist, without showing a particular document of the state of the art disclosing such a composition.

With respect to inventive step, the decision of the opposition division relied on experiments of the respondent that - at least at the date of the oral proceedings - were not indicative because they were contradicted by later filed experimental data of the same party. The inconsistencies shown by the appellant casted so much doubt on all the respondent's data that the convincing series of experiments and resulting data of the appellant prevailed. By these experiments, in particular, amelioration of physical stability (resuspendability) and maintenance of chemical stability as far as required by the authorities for admission as a medicament were demonstrated, both with respect to the closest prior art either in form of the commercially sold "EXCENEL® sterile suspension"

including excipients or in the form of a pure mixture of ceftiofur hydrochloride and biocompatible oil as claimed as basic embodiment in the patent.

The latest experiments of the appellant showed that the claimed effect of improved physical stability could be achieved over the whole scope of the claim with respect to the amount of water being present in the pharmaceutical composition and as far as the knowledge of the person skilled in producing dispersions was applied. Results at odds with that could find their explanation solely in steps used during the production procedure by the respondent, that were not "perfect" in the art of production of dispersions. In particular the phenomenon of caking would have been avoided by the skilled person in routinely optimising the order of the preparation, stirring and dissolution steps.

In addition, to show that there was bad resuspendability it was not sufficient to put a bottle containing a dispersion upside down after storage for a certain time.

With respect to the first auxiliary request, it was to be stated that all experiments of the documents (12) and (20) concerned contents of water not falling under the claimed range.

VII. The respondent's arguments may be summarised as follows:

Based on the knowledge of document (2), a composition disclosed in document (11) would contain a quantity of water falling under claim 1 as submitted by the appellant or would develop to contain such a quantity

of water because of being hygroscopic. Thus, the subject-matter as claimed was not novel.

The experiments of the respondent showed that there was no amelioration of the physical stability of the claimed products and a worsening of the chemical stability in the time of storage, such that the problem of improvement was not solved over the claimed range of water content and under all conditions of preparation of the subject-matter of claim 1.

If this result was to be attributed to a peculiarity of the process of production used by the respondent while remaining well within all limits observed by the person skilled in the art, it is then exactly the proof that the effect claimed by the appellant was not achievable over the whole scope that a product claim would confer.

Thus, the addition of water appeared arbitrary on the basis of document (11) or "EXCENEL® sterile suspension" (document (14)) with regard to document (2) disclosing usual contents of water in ceftiofur hydrochloride. An inventive step could not be established by such a feature.

VIII. The appellant (patentee) requested that the decision under appeal be set aside and that the patent be maintained on the basis of its main request or its first auxiliary request, both filed with letter dated 30 October 2006, or alternatively on the basis of its second auxiliary request filed with letter dated 17 June 2010, or further alternatively on the basis of its third auxiliary request filed with letter dated 15 January 2010.

IX. The respondent (opponent) requested that the appeal be dismissed.

Reasons for the decision

1. The appeal is admissible.

2. *Claim 1 of the main request; Articles 123(2) and (3) (100(c)) EPC, Article 83 (100(b)) and Article 84 EPC*

Claim 1 of the main request can be derived from page 6, lines 25 to 32 in combination with page 7, lines 7 to 9 and page 13, lines 5 to 13 of the application as originally filed.

Since, in comparison to claim 1 as granted, it constitutes a simple narrowing of the range of water content in addition to clarification of the water content per ml of the pharmaceutical composition, there is no objection with regard to Article 123(3) EPC.

The board is satisfied that there is no objection with regard to clarity (Article 84 EPC) since the simple narrowing of the range of water content does not open this article for assessment in opposition proceedings.

As regards sufficient disclosure of the claimed subject-matter under Article 83 EPC, the board sees no reason to depart from the arguments and the positive conclusion of the opposition division in its decision.

3. *Claim 1 of the main request; Article 54 EPC*

3.1 In example 7 in column 13 of document (11) an in vitro dissolution test of an embodiment of example 4 in column 12 is disclosed that contains 100 mg ceftiofur hydrochloride and standard pharmaceutical excipients. Accordingly, since tested for medical dissolution characteristics, this embodiment represents a pharmaceutical composition. It contains ceftiofur hydrochloride and - from the provisions of example 4 - lecithin and sorbitan monooleate together with cottonseed oil q.s.. However, there is no information on water content, which thus is the only feature of claim 1 of the main request not represented in example 7 of document (11).

3.2 In addition, no clear and unambiguous link is contained in document (11), example 7 that ceftiofur hydrochloride was to be used as produced by means of the methods disclosed in document (2). Thus, referring to one of the upper limits of the range of water (or other solvents) content set out in column 3, lines 38 to 40 of document (2) amounts to the introduction of a second document in order to establish lack of novelty, which is not allowed under the EPC.

3.3 Consequently, the objection of lack of novelty does not hold, which undisputedly is also the case with respect to the other documents on file.

4. *Claim 1 of the main request, Article 56 EPC*

4.1 Document (11) represents the closest state of the art.

4.2 The definition of the technical problem underlying the patent in suit relies on the claimed effect, i.e. the improvement of the physical stability of the pharmaceutical formulation in the form of resuspendability while not abandoning the usefulness of the preparation in the pharmaceutical field in the form of the chemical stability of ceftiofur hydrochloride as far as required by the authorities, meaning usually less than 10% decrease in potency during shelf life (see the patent in suit, page 3, lines 4 to 8, page 7, line 54 and page 6, lines 43 to 44 together with page 7, lines 24 to 25). In order to establish a valid basis for the assessment of inventive step, this effect necessarily must be caused by the sole feature in the claim differing from the state of the art, i.e. the amount of water incorporated in the pharmaceutical composition of the claimed invention (see point 3.1 of this decision).

4.2.1 Since claim 1 of the main request concerns a product *per se*, the claimed subject-matter is independent of the manner of its production. *Vice versa*, with respect to the question of patentability based on the claimed effect, this effect also has to be achievable independently, i.e. the product as claimed has to exhibit this effect no matter how it is produced, as far as it is "prepared by any method known in the art for the preparation of injectable suspensions", as inherently confirmed by the appellant via the patent in suit on page 3, lines 41 to 42.

4.2.2 The respondent, in the production of its samples, undoubtedly used another process of preparation than

the appellant. As a reaction to the questions raised by the appellant in its submission dated 15 January 2010, page 6, paragraph 3 and the paragraph bridging page 6 and page 7, the respondent explained its process of production during the oral proceedings. The appellant at least in part commented on differing steps as used in its own process of preparation.

On this basis, the board has no reason to doubt the respondent's professional conduct of its process of preparing the samples of documents (12) and (20).

Consequently, the board finds that the claimed effect of better resuspendability could not be affirmed in the case of application of the process of production as conducted by the respondent, who is a skilled person applying his knowledge with usual care.

As set out in documents (12) and (20), two lots falling under the scope of the claim were assessed: lot B-1 (11,1 mg of water per ml of composition) exhibiting at least no better resuspendability than lot A (2.3 mg/ml) after 15 days and 3 months, and lot B-2 (21.0 mg/ml) exhibiting an even worse one.

Lot A was produced according to document (11) as closest prior art, since the components ceftiofur hydrochloride and biocompatible oil were used as mentioned there without adding water (see document (12), table 1 on page 2). According to claim 1 of the main request, with ceftiofur hydrochloride and biocompatible oil as the only mandatory components in the claimed composition, there was no addition of lecithin and sorbitan monooleate.

4.2.3 Consequently, the effect of better resuspendability is not exclusively caused by the choice of the claimed amount of water alone, but at least also or even only by undefined other effects, e.g. another "method known in the art for the preparation of injectable suspensions". Therefore, this effect cannot be acknowledged as a basis for the problem to be solved when assessing inventive step.

4.2.4 Thus, the problem underlying the invention, i.e. the improvement of the physical stability of the pharmaceutical composition, is not successfully solved by the provision of a pharmaceutical composition characterised by the features of claim 1 of the main request, and has therefore to be reformulated in a less ambitious way.

It is therefore only to be seen in providing a further pharmaceutical composition containing ceftiofur hydrochloride.

4.3 According to claim 1 of the main request, one solution to this problem is the adjustment of the water content in a pharmaceutical composition comprising ceftiofur hydrochloride and a biocompatible oil to 2.5 to 22.0 mg of water/ml of composition.

4.4 The board is convinced that this problem has been solved.

4.5 In column 3, lines 38 to 40 of document (2), however, it is disclosed that ceftiofur hydrochloride based on this process of preparation may contain 0.5% to 7% of

water or other solvents, usually 1% to 3%, meaning in a 1 ml sample according to example 7 of document (11) a content of 100 mg of ceftiofur hydrochloride and as the upper limit 7 mg or 3 mg of water.

Accordingly, the teaching of the application in suit only puts into practice what is already known to the skilled person from document (11) together with document (2); at most, the teaching of the patent in suit presents itself as an arbitrary modification of the preparation of the state of the art (document (11)) with respect to its water content, the variations of which are known from document (2).

4.6 Consequently, the board concludes that the subject-matter of claim 1 of the main request does not involve an inventive step (Article 56 EPC).

5. *First to third auxiliary requests*

It is clear from the argumentation under point 4 of this decision that the claimed effect is not inevitably produced by the claimed content of water in the preparation, this being the sole feature differing from the closest state of the art (first auxiliary request). Taking account of "lecithin and sorbitan monooleate" and "one or more pharmaceutically acceptable excipients" contained as additional features in the second and third auxiliary requests respectively, this still holds true, since "lecithin and sorbitan monooleate" are components in example 7 of document (11) as well and since they represent "one or more pharmaceutically acceptable excipients".

With respect to the subject-matter of the auxiliary requests, the presence of a causal link between water content and claimed effect is still necessary for asserting inventive step, and in the absence of such causality claims 1 of the first, second and third auxiliary requests do not meet the provisions of Article 56 EPC either.

6. Under these circumstances, the additional arguments of the appellant cannot hold.

The inconsistencies within the experiments of the respondent relate to the chemical stability of the ceftiofur hydrochloride and not to the problem of resuspendability. In addition, they only demonstrate that variations of the products used to prepare the composition or variations related to the process of manufacture influence the results, including the presence or absence of the claimed effect.

Even if the contents of water referred to in the experiments in documents (12) and (20) are outside the range of 2.5 to 7.5 mg of water/ml of composition as claimed in the first auxiliary request, one conclusion from these experiments is that the claimed effect of better resuspendability is not caused by the choice of the claimed amount of water alone, this conclusion remaining true even when the upper limit of the **claimed** water content is reduced from 22.0 mg to 7.5 mg/ml of composition.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar:

The Chairman:

N. Maslin

U. Oswald